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by

HENRY L. JAFFE

ALEXANDER B. GUTMAN

I. C. RUBIN

ROBERT S. HOTCHKISS

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TUMORS OF THE SKELETAL SYSTEM: PATHOLOGICAL ASPECTS*

HENRY L. JAFFE

Pathologist, Hospital for Joint Diseases

IN the reasonable assumption that the primary tumors of bone represent the core of my subject, I shall devote my time to these. Before proceeding to the franker tumors, I wish to deal with that peculiar lesion which we have described under the name of osteoid-osteoma. Then I shall take up, in order: giant cell tumor; osteogenic sarcoma, fibrosarcoma, and chondrosarcoma; Ewing sarcoma; and multiple myeloma.

There are, of course, other primary tumors of bone, both benign and malignant. The malignant ones, in particular (such as liposarcoma, angiosarcoma and neurogenic sarcoma), are very rare, and we shall make no further mention of them. With certain of the benign tumors, we shall deal at least in passing, pointing out, for instance, that an enchondroma or an osteochondroma may be the point of departure for a chondrosarcoma. The benign tumors of bone also include hemangioma and neurofibroma. Furthermore, they include a number of other

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lesions which (because they may contain some giant cells), have, in the past, been loosely classed with giant-cell tumor of bone—usually as some form of giant-cell tumor variant. Time does not permit any discussion of the pathology of these various benign tumors of bone. In particular, we shall not be able to consider the pathology of those which, in the past, have been uncritically linked with giant-cell tumor. Time likewise does not permit consideration of the primary tumors of the periosteum per se (which, incidentally, are quite rare), nor of tumors of articular capsules. Also, it does not allow us to consider the many interesting pathologico-anatomic questions relating to tumors metastatic to bone.

Osteoid-Osteoma

An osteoid-osteoma[1] is a very peculiar, small, benign, tumorous lesion developing as a nidus in a bone. When well advanced in its evolution, the lesion consists, in varying proportions, of osteoid and trabeculae of newly formed osseous tissue, set in a substratum of highly vascularized osteogenic connective tissue.

The lesion is by no means rare. It predilects adolescents and young adults. The site of the lesion is found to be a tibia or a femur in about half of the cases, and any one of a number of other bones in the other half. The speaker has not yet observed it in a rib or in the calvarium. In a given affected bone, the lesion may lie within the spongiosa, or against the inner surface of the cortex, or even within the cortex. Though the osteoid-osteoma does not usually exceed a centimeter in its greatest diameter, the total abnormal area in the affected bone may be found considerably extended by a perifocal zone of bone thickening or sclerosis.

The diagnosis of osteoid-osteoma is not very difficult if one is familiar with its clinical peculiarities and if it has advanced sufficiently in its evolution to be demonstrable roentgenographically. Anatomically, if an osteoid-osteoma is removed intact from its setting, or at least removed without being crumbled, it stands out strikingly, especially in the tissue sections. Its complete benignity is attested by the fact that, in no case in which the lesion has been completely removed surgically has there ever been a recurrence, and when it has been removed the complaints (mainly of local pain) cease with dramatic promptness.

Giant-Cell Tumor

As has already been indicated, the term "giant-cell tumor of bone" had long been loosely applied, having been used not only for giant-cell tumor proper, but likewise for a number of other lesions, usually with the qualification "variant." In a systematic study of the question, we[2] have shown that there is no firm pathologic basis for such designations as the "calcifying or chondromatous variant" of giant-cell tumor, the "spindle-cell variant," the "xanthic variant," or the "cystic variant." We have stressed the idea that these so-called "variants" have little in common, clinically and anatomically, with genuine giant-cell tumor, and also little in common with each other except an auspicious prognosis. When, as is increasingly being done, one segregates these so-called "variants" away from the real giant-cell tumor, the latter comes to stand out all the more. One finds it to be a relatively uncommon, highly distinctive tumor, which, far from being consistently benign, often comes to show aggressive qualities.[3]

The age incidence of giant-cell tumor is worth remarking. It is rarely observed in a person under 20 years of age. As to localization, the lesion strongly predilects the ends of long bones. When situated in a long bone, it is usually found implicating some part of an epiphysial end of the bone and the adjacent metaphysis. The presence of more than one giant-cell tumor of bone in the same person (that is, the appearance of this tumor otherwise than as a solitary lesion) is very rare indeed, but the speaker has seen an anatomically proved instance of this.

Especially if not modified by previous treatment, a transected giant-cell tumor intact in its setting (for instance in the end of a long bone) is not likely to be confused with anything else. Furthermore, on the roentgenographic side, it is only rarely that a giant-cell tumor (in a long bone, for instance) shows anything like the multilocular, cyst-like "soap-bubble" appearance which is frequently maintained to be "typical" for it.

Like the gross, the histologic picture of giant-cell tumor is clearly characterized. The viable and otherwise unmodified tumor tissue is composed essentially of a vascularized network of spindle-shaped or ovoid stromal cells, heavily interspersed with multinuclear giant cells. Mainly on the basis of differences in stromal-cell detail, one can grade

the giant-cell tumors in respect to their aggressiveness. Aggressiveness is attested by increase and crowding of the stromal cells, plumping up of these cells, and particularly of their nuclei, the presence of many stromal cells undergoing mitotic division, and the presence of stromal cells with one or more very large nuclei. Along these lines, we subclassify giant-cell tumor into three grades—I, II, and III—showing respectively, no appreciable, moderate, and pronounced atypism of the stromal cells. The giant-cell tumors of grade III present a sarcomatous stroma and are already frankly malignant. Occasionally a malignant giant-cell tumor is already so (that is, a tumor of grade III) when studied for the first time anatomically. Usually, however, grade III represents malignant transformation, through successive recurrences, of a tumor which when first studied, was of grade I or II. The prognosis in cases of giant-cell tumor is very bad, because of its strong tendency to metastasize. Indeed, very often the tumors of grade II already show such local clinical aggressiveness that the affected limb has to be amputated.

Osteogenic Sarcoma, Fibrosarcoma, and Chondrosarcoma

In its revised (1939) classification, the Registry of Bone Sarcoma[4] gives recognition to chondrosarcoma as a tumor entity distinct from osteogenic sarcoma, but still does not recognize the entity of fibrosarcoma of bone. Whether one does recognize fibrosarcoma of bone as an entity depends upon the histogenetic definition which one accepts for osteogenic sarcoma. The Registry defines the latter as a sarcoma derived from the tissue presumably intended to form bone, irrespective of whether it eventually does so. By this definition, fibrosarcoma can logically remain a sub-form of osteogenic sarcoma of bone. On the other hand, in the case of a sarcomatous connective-tissue tumor of bone which fails to express any bone-forming capacity whatever in the course of its full evolution, what evidence is there that the tumor in question has arisen from "osteogenic" and not from neutral or supporting connective tissue? On a strict oncologic basis, it would seem appropriate to designate such a tumor as a fibrosarcoma of bone, and we do.

Osteogenic Sarcoma

It is only as a primary malignant tumor appearing de novo in a bone that osteogenic sarcoma concerns us here. That is, we shall not

consider it in connection with its occurrence as a common complication of Paget's disease of bone, nor are we concerned with extra-skeletal osteogenic sarcoma.

Even apart from its occurrence as a complicating tumor, osteogenic sarcoma is the most common of the malignant tumors of bone. As an independent primary bone tumor, it strongly predilects the age group between 10 and 25 years. It is a tumor with an extremely high mortality rate, no matter how the case is treated. The five-year survival rate in our experience is definitely less than 10 per cent. It is to be suspected that recorded survival rates of 20 or 30 per cent or even more reflect an inclusion, in the reported material, of lesions other than osteogenic sarcoma, and specifically cases of chondrosarcoma, cases of fibrous dysplasia in a single bone, cases representing relatively benign fibrous or osseous proliferations of the periosteum alone, etc.

Osteogenic sarcoma develops most commonly in long bones. In a long bone, the tumor usually involves one end of the shaft and at least part of the adjacent epiphysial area, though sometimes it is situated well toward the middle of the shaft.

Contrary to the statement often made that the tumor takes its departure from periosteum, the fact seems rather to be that it begins its growth in the interior of the affected bone area. However, most osteogenic sarcomas, when first seen, not only involve the interior but have somewhere already penetrated the cortex, to lie beneath the periosteum, or have even perforated the latter in some places and gone on growing beyond it. Irrespective of whether the lesion is still largely confined within the limits of the bone or already lies to a considerable extent beyond these limits, an individual tumor may show relatively little, moderate, or very considerable ossification.

In our series of osteogenic sarcoma, about one quarter were relatively ossified, about one quarter moderately ossified, and one half heavily ossified and considerably eburnated. On the whole, the less ossified the tumor, the more likely it is to show considerable necrosis, cystification, and telangiectasis as secondary features of its pathologic anatomy, though even highly ossified tumors occasionally show considerable telangiectasis, particularly in their more peripheral portions. Prognostic significance has sometimes been attached to the intensity of ossification shown by an individual tumor, but the fact is that, as a rule, the disease reaches its fatal termination about as quickly when

the original tumor is a highly ossified one as when it is not.

Metastasis seems to occur mainly, if not exclusively, by the hematogenous route. Spread of the tumor from the original bone site to the regional lymph nodes seems to be of rare occurrence. Pulmonary metastases are consistently present in the cases which terminate fatally, and death commonly supervenes within two years (and often within a matter of months) from the time when the patient first comes under treatment.

On the whole, osteogenic sarcoma is a lesion relatively easy to diagnose on the basis of the x-ray picture. Difficulties are created largely by those cases in which ossification is slight and the x-ray picture therefore ambiguous. On the other hand, when radiopacity is moderate (that is, fairly well developed, though not dominating the lesional shadow as a whole) a diagnosis of osteogenic sarcoma can already be made with reasonable confidence from the x-ray picture. In regard to the highly ossified and eburnated tumors (that is, frank, sclerosing osteogenic sarcoma) the pre-operative diagnosis on the basis of the x-ray picture becomes even more certain. However, in studying and evaluating the roentgenographic picture in any particular case, even if the lesion shows moderate or intense radiopacity, one must, of course, consider this picture within the framework of the case as a whole. Thus, except in rare instances, if the patient is a child or at most a young adult, the lesion is a solitary one lying toward one end of a long bone, and the shadow it casts is strikingly radiopaque, the lesion is found, on anatomic examination, to be an osteogenic sarcoma. On the other hand, even if the lesion is oriented toward the end of a long bone and casts a strikingly radiopaque shadow and Paget's disease has been ruled out, if the patient is a mature or older adult, the reservation that one may be dealing with some other lesion (for instance an osteoplastic carcinoma metastasis) has to be explored.

Time does not permit more than a few general remarks about the histologic findings in osteogenic sarcoma. In a given lesion, the still unmodified stromal tissue may be composed predominantly of spindle-shaped cells or may be definitely anaplastic and present a highly polymorphous cellular character. Its osteoid and osseous transformation is prepared by collagenization, which spreads irregularly through it. Scattered and focal deposition of calcium in the collagenized stroma then inaugurates the appearance of actual tumor bone. Interestingly enough,

the stromal tumor cells which have become incarcerated in intercellular matrix look less ominous histologically than the cells of the neighboring still uncollagenized and unossified sarcomatous stroma. If the tumor is one whose sarcomatous stroma does not lay down much tumor osteoid and bone, the original osseous tissue(both spongy and cortical) at the site of its growth is subjected from the beginning mainly to resorption and dissolution. If the lesion is one whose sarcomatous stroma does lay down much tumor osteoid and bone, the highly sclerotic and eburnated areas in the interior of the affected bone part are found to result from superposition of ossified tumor tissue upon the preëxisting spongy trabeculae, with consequent obliteration of the spongy marrow spaces. The presence of densely ossified areas of tumor tissue outside of the cortex, especially in these cases, can be shown to be due to the intermingling of actively ossifying tumor tissue with reactive non-tumorous new bone of periosteal origin.

Fibrosarcoma

As noted, we mean by fibrosarcoma of bone a primary connective-tissue sarcoma of bone which does not demonstrate any osteogenic potentialities, either in its local growth or in its metastases. In its anaplastic form, the lesion has a very ominous prognosis, but the more differentiated fibrosarcomas are of lesser malignancy. Its most common site is a long bone of an extremity, where it usually starts its development in the interior of a shaft end. In such a bone, the tumor tissue fills the spongy marrow spaces at the site of its growth and induces more or less lytic destruction of the spongy trabeculae which it encircles. It gains exit by penetrating through the cortex over at least part of the circumference, and finally produces an overlying tumor mass of smaller or larger proportions.

The roentgenographic reflections of these changes are often difficult to interpret, on account of their ambiguity. Thus, if the lytic resorption of the spongy bone is not pronounced, the interior of the affected bone area may present merely vague vacuolation Though it may be plain that the cortex has been broken through in places, the overlying tumor mass, totally lacking osseous tissue, is sometimes difficult to visualize unless soft-tissue technique has been employed. Even when it is clear from the x-ray picture as a whole that one is dealing with a malignant tumor, biopsy is required to delimit its character.

The biopsy specimen will show a connective-tissue sarcoma whose stromal cells may be predominantly spindle-shaped or, on the other hand, rather polymorphous, but in either case fails, of course, to show tumor osteoid and bone developing in the stroma. It is clear that from such an examination alone one cannot be sure that one is dealing with a fibrosarcoma and not with a still-unossified area of an osteogenic sarcoma. If one is to be sure, ample sampling of the amputation specimen must have shown beyond a reasonable doubt that the tissue is non-osteogenic throughout. In such cases, furthermore, the metastases, too, will prove to be non-osteogenic, thus sustaining the interpretation of the original lesion as a fibrosarcoma.

Chondrosarcoma

As a malignant tumor arising from already preformed cartilage, chondrosarcoma[5] stands apart histogenetically from osteogenic sarcoma and fibrosarcoma of bone. Indeed, in regard to a given chondrosarcoma, it is often possible to show or deduce from the roentgenographic and pathologic findings that it has arisen from an originally benign cartilage growth, and specifically from an enchondroma (in a case of solitary or multiple enchondroma of bone) or the cartilage cap of an osteochondroma (in a case of solitary or multiple osteocartilaginous exostosis).

The incidence of chondrosarcoma of bone is somewhat less than half of that of osteogenic sarcoma. The patients are usually between 25 and 50 years of age, and only occasionally are they still in their teens. Long bones, innominate bones, and ribs, in descending order of frequency, seem to be the most common sites for development of the lesion.

For gross anatomic orientation, a chondrosarcoma which begins its development in the interior of a bone is often denoted as a central chondrosarcoma, and one which begins in the cartilage cap of an exostosis as a peripheral chondrosarcoma. A central chondrosarcoma usually gains exit from the bone slowly, and where it is penetrating the cortex, the latter may even thicken. After issuing from the bone, the proliferating tumor tissue invades the overlying soft parts, producing larger or smaller tumor masses attached to the bone. The tumor cartilage in the interior of the bone may or may not have focal areas of calcification and ossification, but the tumor cartilage around the bone is strikingly lacking in these respects. In particular, where the tumor

tissue outside of the cortex is unmodified (by hemorrhage, mucoid degeneration, or cystification) it is composed of smaller or larger facets of glistening white cartilage.

As to peripheral chondrosarcoma, it is interesting that, even when reaching a large size, the tumor tends to retain some sort of cartilage cap, however exuberant and irregular in outline, thus still suggesting in its outward appearance, though in a distorted way, an osteocartilaginous exostosis. Its cap is demarcated in places by an endochondral ossification line from the deeper portion of the growth, which is composed of islands of cartilage and is always heavily interspersed with foci of calcification and ossification.

It is sometimes a matter of years before a cartilage growth which is undergoing malignant transformation has reached a stage in which the cytologic picture of the tumor expresses obvious full-fledged malignity. This is manifested in pronounced cellularity of the tumor tissue, and a general plumping of the nuclei of the cartilage cells. Also, many of the cartilage cells, though still relatively small, are binuclear, while many giant cartilage cells with large, bizarre single and multiple nuclei are also to be seen. Before this stage is reached, the lesion is likely to be "underdiagnosed" by the pathologist if he does not appreciate the significance of subtle evidence of atypism of the cartilage cells, tending in this general direction and already discoverable, at least in some fields, in the lesional tissue submitted to him.

Clinically, even after the tumor has reached full-fledged malignity, it often still remains locally invasive for a long time, although exceptionally a case may run a fulminating course. All this makes it clear why, in general, chondrosarcoma is a tumor so much less immediate in its threat to life than osteogenic sarcoma or fibrosarcoma of bone. In fact, if the lesion is in a site accessible to surgical intervention and the latter is not "too little and too late," a fairly good prognosis can be offered for the case in question.

When breaking its local bounds, whether sooner or later, the tumor spreads by irrupting into the regional venous channels and continues its growth in the major veins draining the part, without necessarily adhering very much to the vessel walls. Eventually it may extend to the heart and lungs in cord-like plugs, but often no parenchymal metastases are found at autopsy. In other cases, it does give rise to parenchymal metastases, at least in the lungs, though rarely to other organs.

Ewing Sarcoma

Contrary to the belief held in some quarters, our experience supports the idea that a primary bone tumor entity corresponding to what Ewing attempted to single out does exist.[6] The tumor is not a particularly common one, and the patients are mainly in the age group between 10 and 25 years. The presenting lesion (that is, the one causing the complaints which lead the patient to seek medical care) is most commonly in a long bone or one of the bones of the trunk— very often an innominate bone. The idea that the presenting bone lesion shows a characteristic, if not typical, roentgenographic picture of high diagnostic value does not stand up under close scrutiny.

At the time when the presenting lesion is first identified as a Ewing sarcoma, x-ray examination of the entire skeleton usually fails to reveal evidence of tumor in the other bones. Even under these circumstances, however, there is no doubt that in some cases the marrow spaces of many of the bones already contain tumor tissue. Clinically, in a given case, persistent mild fever, secondary anemia and an increased sedimentation rate of the blood can be taken as evidence of this, whether or not sufficient lytic destruction of spongy bone and cortex has taken place to show up in the x-ray films. As autopsy discloses, the evolution of the disease is regularly associated with widespread involvement of the skeleton, practically all the bones eventually becoming riddled through with tumor tissue. Even just before death, however, the x-ray findings hardly reflect the severity of the actual involvement. Of the internal organs, the lungs bear the brunt of the metastases. Altogether, Ewing sarcoma is a disease having a most doleful prognosis, it being doubtful whether there is more than an occasional instance of survival in an unequivocal case.

Beyond the fact that it is a specific malignant tumor primary in bones, there is still much to be learned about Ewing sarcoma in respect to its histogenesis. We incline toward Oberling's idea that the tumor cells of the Ewing sarcoma are derived from the supporting framework (the reticular tissue) of the bone marrow—a framework which can be regarded as a mesenchymal or primitive form of connective tissue. This idea does not support Ewing's own contention that the tumor cells are derived from capillary or vascular (or perivascular) endothelium.

In well-preserved tumor tissue, the cells appear in a sort of net-

work, lack delimiting membranes, are connected by short or long cytoplasmic processes, and have a fairly large, round or oval nucleus showing scattered chromatin. The often stressed perivascular orientation (so-called perithelial arrangement) of the tumor cells is likewise not a characteristic cytologic feature of the tumor, although it may be observed in tumor areas which have become heavily invaded by blood vessels, especially in the wake of hemorrhage. Furthermore, the formations suggestive of rosettes have been overstressed as part of the cytologic picture. When, in an occasional lesion, one finds formations in which cells show ring-like arrangements (though not around a vessel) these formations can be seen to have resulted from degeneration of centrally located cells whose shadows are still perceptible.

Finally, it is necessary to stress the idea that diagnosis of Ewing sarcoma from a biopsy specimen, even if the latter is obtained by surgical incision, has to be made with great circumspection, because of the numerous possibilities for error. If one observes proper caution, the diagnosis of Ewing sarcoma will not be pronounced too often, but will be made with a discrimination which will help to do away with the disappointment of not having autopsy confirm the diagnosis made on the basis of biopsy findings.

Multiple Myeloma

Unfortunately, time permits only a few general remarks about multiple myeloma. This is a distinctive primary cancer apparently taking its departure from the myeloid-formative tissue proper. Anatomically, practically every bone may ultimately come to be involved, more or less, in a given case. Progress of the disease over the skeleton may be steady and rapid, sometimes from the beginning and sometimes after a static period. One gathers also that in some cases, before the disease becomes spread over the skeleton, it may flourish in one bone (as a so-called solitary myeloma) for months or even years. It is only seldom that the disease shows any metastatic spread whatever to the viscera or lymph nodes.

It is associated, however, with almost pathognomonic cytologic changes in the kidneys. Specifically, the latter almost constantly show plugs of proteinaceous material (often surrounded by foreign-body giant cells) in the renal tubules in the cases coming to autopsy. The plugging tends to lead to tubular atrophy and also to interstitial scar-

ring, and, if widespread, to renal insufficiency, sometimes very severe. In cases in which such renal changes are found at autopsy, the patient may or may not have shown Bence-Jones proteinuria and hyperproteinemia during life. The kidneys, and specifically the tubular epithelium and interstitial connective tissue, often also show deposits of calcium granules, and in some cases the metastatic calcifications may be quite heavy and widespread, involving, in addition, the interstitium of the lungs, the lining of the stomach, and even other tissues. This is not at all surprising in view of the relative frequency of hypercalcemia[7] (connected with the lytic resorption of the bones) and the tendency toward renal failure in many of the cases.

Another arresting feature of the pathologic anatomy of multiple myeloma is the presence of amyloid in some cases. So far as the skeleton is concerned, if amyloid is found, it usually presents as scattered deposits detectable only microscopically in the neoplastic tissue of the affected bones. In an occasional case, however, one may find not only the microscopic deposits, but large agglomerations of amyloid, substantially replacing large myelomatous tumor foci. On the other hand, we observed a case of so-called atypical amyloidosis with myeloma in which autopsy failed to reveal evidence of amyloid in the myelomatous tissue itself, though practically all the extra-skeletal tissues and organs, including the voluntary muscles, were heavily infiltrated with amyloid.

It would be futile to attempt to do justice here to the gross appearance of the bones as one notes it in one case or another of multiple myeloma coming to autopsy. It does seem worth while to point out, however, how often one finds multiple myeloma presenting itself clinically because an exuberant focus of the disease has developed in a vertebral body (or several contiguous bodies). In these cases indeed the tumor tends to transgress them, often producing pressure on the cord or local nerve trunks, with the resultant symptoms. In such cases, roentgenographic examination of the rest of the skeleton (including the skull) often fails to reveal the clear-cut punched-out rarefactions which are conventionally held to distinguish the roentgenographic picture of multiple myeloma. It is in such cases (especially if one dorsal or lumbar body alone is clearly affected) that the true nature of the disease often goes unrecognized for long periods, the lesion frequently being interpreted as a local one such as a hemangioma, giant-cell tumor, or Kümmel's-disease fracture, or, if grossly destructive, as a focus of meta-

static malignancy. The true nature of the disease in these cases may become clear if a sternal marrow puncture is done, or when serial x-rays of the rest of the skeleton finally demonstrate widespread lesions in other bones suggesting multiple myeloma, but sometimes it is discovered only at autopsy.

A somewhat special interest attaches to the calvarium. Great emphasis is usually laid upon the diagnostic value of several or even many roundish punched-out rarefactions in x-ray films of the skeleton. It is true that when x-rays show clear-cut and widespread involvement of the rest of the skeleton, in the form of numerous punched-out rarefactions, the calvarium, too, is quite likely to show these, though not infrequently it does not. However, precisely when one turns to the films of the calvarium because the films of the other bones do not show the conventional picture of multiple myeloma, the calvarium too fails to show it. Whether or not the calvarium shows rarefactions in the films, histologic examination will reveal that the marrow of the diploic spaces has been substantially replaced by the tumor tissue. At sites of clear cut rarefactions, one will find that the tumor tissue is present as a nodule which has encroached upon and destroyed the diploic bone, sometimes also thinning the tables, but, in our experience, the tables are seldom perforated, even in such sites.

As to the cytology of the tumor cells proper, it has been recognized and must be emphasized that the cytologic picture is not the same in all cases of multiple myeloma. Roughly, however, they can be fitted into two general cytologic groups. On the one hand, there are the cases in which the tumor cells are predominantly small and bear a superficial resemblance to plasma cells. In these cases, they are roundish and have a stippled nucleus substantially filling the cell. Interspersed among them may be some cells which, though of the same general character, are larger in respect to both cytoplasm and nucleus. It is to the myelomas showing this cytology that the name "plasma cell myeloma" or "plasmacytoma" is commonly applied.

In the other group of myelomas, the cytologic picture tends to be dominated by cells larger than those resembling plasma cells but may be a rather variegated one. The dominant cells in the tumors of this group generally exceed the myeloblast in size and, on the whole, show fairly abundant cytoplasm and have a large, round, oval, or even reniform, pale, stippled nucleus. However, in any particular tumor site

examined, one may also find some of the smaller cells resembling plasma cells, or, on the other hand, find cells which are much larger than the dominant ones and usually show nuclear atypism. Specifically, such atypical cells may present large and hyperchromatic nuclei, giant nuclei of bizarre shape, or two or more nuclei.

Summary

This presentation of the pathologic aspects of tumors of the skeletal system deals only with the primary tumors, and specifically only with: osteoid-osteoma; giant-cell tumor; osteogenic sarcoma, fibrosarcoma, and chondrosarcoma; Ewing sarcoma; and multiple myeloma. Even as to these, only the minimum essentials of the pathology could be given, but, as much as possible, this was correlated in a practical way with the x-ray picture and the clinical course of the condition.

The high-light of osteoid-osteoma is the surprising amount of pain and disability caused by this small lesion, and the promptness and permanence of the relief when it is completely excised.

As to giant-cell tumor, we stressed the fact that when one segregates from it the so-called giant-cell tumor variants, the tumor is found to be one which should not be taken lightly, since it often comes to show aggressive qualities.

In regard to osteogenic sarcoma, emphasis was laid on the definition of this as a connective-tissue sarcoma of bone in which the stroma actually forms some osteoid and osseous tissue in the course of the tumor's evolution. On this basis, fibrosarcoma of bone—a primary connective-tissue sarcoma which does not demonstrate any osteogenic potentialities either in its local growth or its metastases—is regarded by us as an independent entity, and not as a sub-form of osteogenic sarcoma.

It was pointed out that chondrosarcoma stands apart histogenetically from osteogenic sarcoma and fibrosarcoma, since it arises from already preformed cartilage, that it is slow in reaching full-fledged malignity, and that, if accessible to surgical intervention, it has a much more auspicious prognosis than either osteogenic sarcoma or fibrosarcoma of bone.

As to Ewing's sarcoma, we incline toward Oberling's idea that the tumor cells are derived from the supporting framework (the reticular tissue) of the bone marrow—a framework which can be regarded as a mesenchymal or primitive form of connective tissue. It was also brought out that in well-preserved Ewing tumor tissue the cells appear in a

sort of network, lack delimiting membranes, are connected by short or long cytoplasmic processes, and have a fairly large, round or oval nucleus showing scattered chromatin, and that, on the other hand, "perithelial arrangement" and "rosette arrangement" of the tumor cells are fortuitous and have been overstressed.

Finally, in regard to multiple myeloma, it was pointed out that often this presents itself clinically because an exuberant focus of the disease has developed in a vertebral body (or several contiguous bodies) and that in such cases roentgenographic examination of the rest of the skeleton (including the skull) often fails to reveal the clear-cut punched-out rarefactions which are conventionally held to distinguish the roentgenographic picture of multiple myeloma.

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* This article deals with the lesions which have sometimes been called "giant-cell variant of bone cyst or osteitis fibrosa", "healing variant of giant-cell tumor", "xanthic variant of giant-cell tumor", etc.

TUMORS OF THE SKELETAL SYSTEM: MEDICAL ASPECTS*

ALEXANDER B. GUTMAN

Assistant Professor of Medicine
Columbia University, College of Physicians and Surgeons

ALL too often the internist or general practitioner is apt to feel that the problems presented by tumors of the skeletal system do not come within his province and should be relegated to one or another specialty. This attitude may have unfortunate consequences. It is usually the family doctor or the physician concerned principally with internal disease whom the patient with early manifestations of bone tumor first consults. The awareness of the physician and the promptness with which he institutes the measures necessary for the diagnosis and treatment may be deciding factors in determining the subsequent fate of his patient.

This special responsibility arises from the circumstance that the first indication of bone tumor, whether malignant or benign, primary or secondary, is apt to be pain. Usually the pain is localized to the site or sites of skeletal involvement, and it may be possible to elicit tenderness on pressure over the involved bone. In more generalized types of skeletal involvement, however, particularly in the older age groups, the initial complaints may be diffuse and confused with "rheumatism" or "old age." In the case of vertebral involvement and root pain, the complaint may be referred to the corresponding distant area; sciatic distribution of pain, so often misdiagnosed, is a classic example. As a rule, movement of the affected part, or weight-bearing, causes exacerbation of pain which the patient recognizes as deep and not superficial and often as originating in the bony structure. Restriction of mobility and splinting, if already present, help to localize the lesion. Inspection and palpation may reveal a swelling recognizable as of bone because of its location, hardness and immobility. Palpation may also elicit a parchment-like crackling, particularly in central giant-cell tumors and bone cysts. The pain may be indicative of a fracture, so often not preceded

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.
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by overt trauma, and frequently the first indication of skeletal involvement.

While pain often is the initial symptom of bone tumors, the onset may be painless and insidious, characterized by anemia, weight loss, fever and other systemic symptoms which may present great difficulty in diagnosis.

The differential diagnosis of bone tumors necessitates careful history-taking and physical examination, roentgenographic study with expert interpretation, chemical studies of the blood and often final recourse to biopsy. I should like to devote the major part of the time allotted me to a discussion of the role of chemical studies of the blood since these represent a comparatively recent development, with potentialities which frequently are not fully exploited even when the necessary laboratory facilities are available. The discussion will be confined largely to a consideration of the indications for and rationale of the relevant estimations, and to the principles and mechanisms involved. I shall not attempt any systematic classification of bone disease on the basis of chemical findings in the blood.

The blood constituents of principal importance in the differential diagnosis of bone disease are calcium and inorganic phosphate, the major mineral components of bone; the enzymes alkaline phosphatase and acid phosphatase; and the serum proteins. The normal range of these components, together with the general significance of increased or decreased serum levels, are indicated in Table I.

The normal range of serum calcium is generally stated to be 9 to 11 mg. per cent, though the variation actually observed in most normal individuals is within more narrow limits, about 10.2 to 10.9 mg. per cent, and is maintained within these limits with remarkable constancy. In most cases of bone tumor the serum calcium level is not disturbed significantly. The disorders in which definite hypercalcemia occur are few in number, all associated with such rapid, widespread dissolution of bone that calcium salts are poured into the bloodstream even faster than they can be excreted or deposited. In fact, the finding of marked hypercalcemia is so uncommon as to have definite diagnostic value, usually indicative of hyperparathyroidism, hypervitaminosis D, multiple myeloma or osteolytic bone metastases. In multiple myeloma, hypercalcemia occurred in one-third to one-half of the cases in the literature and, as seems clear now, is not related to the serum globulin or Bence-

TABLE I

BLOOD CONSTITUENTS IMPORTANT IN THE DIFFERENTIAL DIAGNOSIS OF BONE DISEASES

	Normal range	*Significance of increased blood levels*	*Significance of decreased blood levels*
Calcium	9-11 mg. %	Rapid, wide-spread mobilization of bone salts (hyperparathyroidism, osteolytic bone metastases, multiple myeloma, hypervitaminosis D).	Hypoparathyroidism; impaired absorption of calcium from the gastrointestinal tract; increased demands in pregnancy and lactation.
Phosphate, inorganic	2.8-4 mg. %	Renal insufficiency; secondary hyperparathyroidism; hypoparathyroidism; multiple myeloma; obstructing tumors of the genitourinary tract with bone metastases.	Vitamin D deficiency (rickets, osteomalacia); hyperparathyroidism; sprue; impaired reabsorption by renal tubules.
Phosphatase, alkaline	1.5-4.0 Bodansky units %	Markedly increased osteoblastic activity (Paget's disease, rickets, hyperparathyroidism, osteogenic sarcoma, osteoplastic bone metastases); biliary tract obstruction (obstructive jaundice, liver metastases).	
Phosphatase, acid	1-3 units %	Metastasizing prostatic carcinoma	
Serum proteins	Total proteins: 6-8 gm. % Globulins: 1.5-2.5 gm. % Bence-Jones protein: 0	Certain chronic infections (lymphogranuloma venereum, kala-azar, sarcoid, etc.); hepatic cirrhosis; multiple myeloma.	Serum albumin decreased in malnutrition, nephrosis, cirrhosis

TABLE II—CASE S.H., AGE 73

METASTASIZING PROSTATIC CARCINOMA (PROSTATECTOMY APRIL 1937)

Date	*Serum acid phosphatase* (units/100 cc.)	*X-ray findings*	*Clinical comment*
April 1938	5.6	Osteoplastic metastases to pelvis and spine	Bone pain
Feb. 1939	14.4	Further spread of metastases	Radiotherapy
May 1939	13.5		
Dec. 1939	31.3	Further spread of metastases	
July 1940			Died

Jones protein content of the blood, but to the extent and rapidity of bone destruction. Hypercalcemia is found in association with metastatic skeletal involvement only when there are extensive bone metastases that are osteolytic in character and rapidly progressive. Carcinoma of the breast, bronchogenic carcinoma and hypernephroma are the most common primary tumors giving rise to osteolytic bone metastases and the finding of hypercalcemia may be helpful in establishing the presence of these tumors.

The normal inorganic phosphate content of serum, expressed as phosphorus, varies from about 2.8 to 4 mg. per cent in the adult. The significance of elevated and depressed levels is indicated in Table I. The determination is helpful in the differential diagnosis of bone tumors chiefly in the recognition of hyperparathyroidism, in which serum phosphate is low so long as there is no significant renal damage with phosphate retention. Multiple myeloma is one of the few tumors destructive of bone in which there may be accompanying damage to both kidneys, with phosphate retention in the blood; this is due to obstruction of tubules by the precipitation out of Bence-Jones protein or other abnormal proteins in the urine undergoing concentration by reabsorption of water in the tubules. Prostatic carcinoma metastasizing to the bones may also cause hyperphosphatemia through obstruction of the bladder neck by growth of the primary tumor.

The alkaline phosphatase activity of normal blood serum in the adult varies from about 1.5 to 4 Bodansky units per 100 cc. So far as known, most of this enzyme is derived from bone-forming cells in bone and calcifying cartilage. The enzyme appears to function at the surface of these cells and is then excreted, being transported by the lymph into the bloodstream, passing through the liver into the bile. There are two general conditions in which the alkaline phosphatase activity of the blood is significantly increased: (1) when there is markedly increased osteoblastic activity leading to increased formation of the enzyme; (2) when the biliary tract is obstructed so that the excretory pathways through the liver are blocked and retention of the enzyme in the bloodstream results. The primary bone tumor most likely to cause increased alkaline phosphatase activity of the serum is osteogenic sarcoma and determination of the enzyme is helpful both in the diagnosis of osteogenic sarcoma and in following the results of treatment. Increased values are observed also in association with osteo-

TABLE III

EFFECT OF CASTRATION ON SERUM ACID AND ALKALINE PHOSHATASES IN TWO PATIENTS WITH METASTATIC PROSTATE CARCINOMA

(Case T.B. Did Well Clinically, Case L.B. Died in 5 Months)

	Case T. B.		*Case L. B.*	
	Acid Phosphatase, Units per 100 cc.	*Alkaline Phosphatase, Bodansky Units per 100 cc.*	*Acid Phosphatase, Units per 100 cc.*	*Alkaline Phosphatase, Bodansky Units per 100 cc.*
Preoperative	80.6	43.3	44.8	12 4
Postoperative				
2 days	68.6	31.6	45.8	9.8
5 days	42.2	31.1	37.0	12.1
1 week	21.1	38.3	35.0	15.1
2 weeks	....	....	39.3	17.3
3 weeks	7.4	52.1	42.5	15.2
4 weeks	....	....	35.7	12.0
8 weeks	3.0	23.7	59.0	10.2
12 weeks	4.1	13.4	393.0	23.6
16 weeks	3.6	8.3	740.0	33.9

TABLE IV

RESULTS OF CASTRATION FOR METASTASIZING PROSTATIC CARCINOMA IN 56 CASES FOLLOWED 6 MONTHS TO 2 YEARS

	After 6 months	*After 1 year*	*After 1-½ yrs.*	*After 2 years*
Total no. cases	56	40	25	14
Lost to follow-up	3	2	2	1
Available for analysis	53	38	23	13
1. Died	6*	8	3	2**
2. Surviving	47	30	20	11
a. markedly improved	38	23	15	5
b. moderately improved	6	4	4	2
c. not improved	4	3	1	4

* 1 death due to myocardial infarction, another to perforated peptic ulcer.
** 1 death due to myocardial infarction.

plastic metastases to the bones, most commonly secondary to prostatic carcinoma. Metastatic involvement of the liver is also frequently associated with some increase in serum alkaline phosphatase activity and the determination sometimes is helpful in the early detection of spread of cancer to the liver.

The acid phosphatase activity of normal blood serum varies from 1 to 3 or 4 units per 100 cc., as determined by an adaptation of the King and Armstrong method we have proposed. Increased values are found in approximately 85 per cent of patients with metastasizing prostatic carcinoma, the blood level usually rising as the tumor spreads (Table II).

The determination of serum acid phosphatase has proven consistent and specific enough to be helpful in the following clinical applications:

1. Corroboration of the clinical diagnosis of metastasizing prostatic carcinoma.
2. Indicating spread of prostatic carcinoma before this may be demonstrable by x-ray.
3. Determining prostatic or non-prostatic origin of tumor in patients known to have metastases.
4. Differentiating Paget's disease from metastatic prostatic carcinoma.
5. Selection of cases for radical prostatectomy.
6. Follow-up of the results of castration and of treatment with estrogens.

The use of the determination in following the patient's course after castration is indicated in Table III where Case T.B. illustrates the findings when amelioration of symptoms is prolonged, Case L.B. when castration is followed by no symptomatic improvement. Table IV summarizes the clinical results of castration in 56 patients followed at the Presbyterian Hospital over a period of two years.

The determination of serum proteins is often helpful in the diagnosis of multiple myeloma since over half of the cases reported in the literature show hyperproteinemia. The increase may involve both the euglobulin fraction and the pseudoglobulin fraction (as determined by Howe's method) and may thus be indistinguishable from that observed in certain chronic infectious diseases except that the total protein level may be so high as to exclude most of them. In some instances of multiple myeloma peculiarities in the salting-out behavior of the proteins, due to the presence of Bence-Jones proteins and other ab-

normal proteins, may be noted and these are virtually pathognomonic. Marked hyperglobulinemia without any increase in the euglobulin fraction is a characteristic finding which occurs frequently enough to be of diagnostic importance. Corresponding atypical electrophoretic patterns may be equally distinctive.

In this discussion of the medical aspects of tumors of the skeletal system, little has been said about medical treatment. The reason for this omission, of course, is that apart from supportive therapy and amelioration of pain, medical management has little to offer in the treatment of most bone tumors; for the present, the chief function of the internist is to recognize and classify tumors of bone early enough for effective surgical intervention or radiation therapy. There are indications, however, that medical treatment may play a more important role in this field. Estrogen therapy in prostatic carcinoma, androgen therapy in cancer of the breast, the use of nitrogen mustards in the lymphomas, and other recent advances which have been discussed by previous speakers in this series, are examples of the present trends.

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DIAGNOSTIC PROCEDURES IN THE INVESTIGATION OF STERILITY IN THE FEMALE: EVALUATION OF THEIR CLINICAL IMPORTANCE*

I. C. RUBIN

Clinical Professor of Gynecology
College of Physicians and Surgeons, Columbia University

MODERN investigation of sterility and infertility has become a highly specialized discipline, the object of which is to detect the causes responsible for the fruitless mating. As nearly everyone knows by now it involves inquiry into the anatomical, physiological and pathological factors of each partner joined in barren marriage. In many instances search for the cause or causes is analogous to tracking down the "criminal and his accomplices in a detective story" so elusive and uncertain may be the underlying factors and so tenuous the clues. Yet not uncommonly it is a trifling matter, one not ordinarily considered that may be at the basis of the failure to conceive.

A few examples may be cited. There is the couple who through gross misinformation habitually selects the wrong time for "fruitful copulation"—the woman who douches immediately after coitus for cleanliness, one who immediately urinates after the sex act. Couples in their ardor not to miss the favorable time resort to too frequent intercourse thus exhausting spermatogenesis and missing the supreme opportunity, when ovulation takes place. Daily douching with an antiseptic solution without need when local conditions are normal is another cause of failure to conceive.

Unnecessary contraception in the presence of natural barriers has recently been stressed in a special communication based upon an analysis of 686 married women who practiced contraception for varying lengths of time.[1] There are many other such impediments which may be revealed by careful and comprehensive history taking. The suggestive data are not always volunteered by the patient, sometimes coming

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to the surface quite by accident. Correction of errors of sex hygiene may be all that is needed in these cases. Faults of sex hygiene on the male side I leave to the urologists to deal with.

It is obvious therefore that the first step in the investigation of a sterile mating is to get a good medical history of both partners. As I am dealing with the female side of sterility I shall dwell upon the gynecological aspects but many of the constitutional factors are of equal importance in both sexes.

Mumps is of particular etiologic importance. It affects the ovaries as well as the testes. Even mild attacks in adolescence may be followed on one side by amenorrhea and on the other by failure of spermatogenesis. Scarlet fever, streptococcic sepsis and other infectious diseases of childhood may leave the ovaries damaged in later life. Appendicitis of all degrees of severity should not be overlooked as responsible for tubal occlusions and periovarian adhesions. Peritoneal tuberculosis, pneumococcic peritonitis, operative interventions for acute abdominal lesions are other noteworthy data. An attack of vulvovaginitis in early childhood is in my experience not as significant as has been generally supposed. Prolonged and unnecessary local treatments for this condition nowadays happily unnecessary may be responsible for some vaginal atresias and cervical phimosis.

Developmental retardation chiefly physical but also mental, has endocrine significance. Late development of teeth, late menarche and prolonged delay in the menstrual habit are more specifically suggestive of deficient endocrine balance and function. Prolonged uterine bleeding of puberty extending into early adult life is also an important symptom of endocrine imbalance in which the pituitary and ovaries manifest a disturbed reciprocal influence.

Notation of these conditions is significant for formulating prognosis and estimating the contributory causes of sterility.

Dietary habits may well be scrutinized as well as the degrees and forms of exercise. Obesity and malnutrition, especially the latter, play an important role in sterility. The effect in either case is upon the germinative zone of the ovarian cortex reducing markedly the ripening of follicles and inhibiting ovulation. Severe mental strain, close application to college studies without a moderate amount of fresh air and some open air exercise also impair fertility.

Similarly the strain and stress to which female executive heads are

subjected has a baneful influence on their fertility. Strenuous factory work undoubtedly impairs ovarian function also. Chronic lead poisoning and other metallic intoxications; absorption of noxious chemical substances which affect the ovaries particularly must be borne in mind. The more young women and especially the older women still in the reproductive age who are employed in industries which expose them to these toxic substances, the greater will be the general incidence of infertility. Sometimes less strenuous exposure as for example painting in oil, which is indulged in as a serious hobby and not ordinarily inquired into, may have a pernicious effect. Female teachers exhibit a conspicuous lowered fertility, partly due to protracted celibacy, but mostly to the strain of their work.

The matter of age is important as the reproductive ability has long ago been recognized to wane decidedly after the fourth decade of life. Though a substantial percentage of women between the ages of 35 and 45 become pregnant, conceptional incidence is certainly small by comparison with younger women between the ages of 20 and 25. Nevertheless women of the older age group should not be discouraged from taking advantage of a sterility investigation which they deserve and need as much or more than their younger sisters.

The degree of fertility of the parents of the sterile woman and of her sisters and brothers and of the husband's family is of genetic interest but not as a rule illuminating to the clinician. Many of my patients are members of large families and may be the only ones in the family group who have not conceived. More important is the particular mating of the individual and the constitutional and genital status of each partner.

Exceptionally abnormal sex development is duplicated by several members of the same family. For these individuals little if anything can be done.

Nor is the matter of libido, or orgasm, or frigidity, as important in lowering fertility as Kisch, amongst others, has led us to believe. Unless these psychosexual abnormalities interfere with the sex act itself they are relatively unimportant as sterility factors. If, however, there are associated stigmata of under-development, their etiological importance may be considerable. The present writer has encountered women who have manifested definite homosexual tendencies and who have nevertheless been highly fertile; and others with bisexual proclivities have also be-

come easily pregnant. However, systematic inquiry into this group of women may be resumed anew in light of all the sterility factors now recognized in combination with the latest techniques of psychoanalysis.

In the group of secondary sterilities the matter of spontaneous abortions, of premature births, of prenatal and postnatal stillbirths unattended by trauma are data which suggest luetic infection, endocrine or vitamin deficiencies or a combination of these which are ultimately reflected in poor germ plasma—while the serological status of the mates as expressed in the Rh factor may show them to be incompatible. Induced abortion and puerperal infection, especially the former, produce sequellae which are likely to impair tubal patency and ovarian function. Anemia per se apparently does not predispose to sterility and infertility. It is frequently encountered in pregnant women. Pulmonary tuberculosis is notoriously associated with pregnancy.

The exact nature of the deterrent is not always determinable. Yet conception can take place in the presence of cervical cancer, of cervical gonorrhea and as serious a metabolic condition as diabetes, although diabetic women statistically show a relatively lowered incidence of pregnancy and greater tendency to stillbirth. The secondary effects of gonorrhea are predominantly sterilizing. Perhaps more careful clinical observation may lead to clues which biologic methods may eventually utilize to explain the mechanism of at least some of these physical and chemical sterility factors. There is need for greater clinical study and analysis to keep pace with the rapid strides made in biophysics and biochemistry.

While we await such progress we are in a much better position today to evaluate the causative factors than at the turn of the present century. Many here can appreciate the advances that have been made in the examination for sterility. Previously it was customary to examine only the woman. A bimanual examination with or without the use of a speculum or uterine sound was depended upon for the verdict of sterility or fertility. Too frequently it happened that the woman who was told "there was nothing the matter with her" and therefore she could expect to conceive never became pregnant while others who were "doomed" to hopeless barrenness left the gynecologist's office disconsolate but to their surprise and great satisfaction became promptly pregnant.

We have not as yet solved all the causes of sterility even today but

we are more aware of the factors involved.

Investigation of the married partners separately and estimation of their combined index or degree of fertility have been rewarded by greater success than was possible previously. One of the first advances in human sterility was the Huhner test. Huhner popularized in the early decade of the present century, the procedure which was first proposed by Marion Sims in the last century, namely the search for spermatozoa in the female genital canal as a test for male potency. This procedure which is indispensable in the investigation of the childless couple will probably continue to belong to the task of the gynecologist. although the coöperation of the urologist is paramount if further advances are to be made in estimating the procreative ability of the male. Since the Huhner test was established, progress on the gynecological side has been made along several aspects hitherto ill understood or not at all.

The first is the cyclical changes in the vaginal mucosa which are related to estrogenic and gonadotrophic function. The second is the character of the cervical mucus secretion which is also subject to cyclical change under the same influence. The third is the cyclical changes in the endometrium now definitely correlated with estrogenic and progesterone secretions. Though Hitschman and Adler described the histologic changes of the uterine mucosa nearly 40 years ago rediscovering and amplifying, according to Hamblen, the observations of Kundrat and Engelman in 1873, the hormonal significance of these endometrial changes was more fully realized some twenty years later. The fourth step in progress was the realization that the fallopian tubes, previously an indeterminate factor playing as they do an important role in the transportation of ova and spermatozoa, became susceptible of determination first by uterosalpingography and shortly afterward by uterotubal insufflation. The fifth and final step in the progress of the knowledge of the genital sphere was the recognition of the fact that ovulation and menstruation do not necessarily go together; that contrary to the old dictum "without ovulation no menstruation," we now know, thanks chiefly to Corner and his group, to Carl Hartmann, Hamblen, Mazer, E. Novak, Rock and Hertig and many others, that menstruation can take place without the precedence of ovulation; in other words that menstruation can be *anovular.*

The techniques that have been developed to determine the event of ovulation have engaged the serious attention of many workers in the

study of sterility. I should like to consider the progressive steps in the order mentioned.

The vaginal mucosa undergoes cyclic morphologic change similar to the change exhibited by the endometrium. Evidence of this cyclical metamorphosis is based upon (a) biopsies of vaginal mucosa, (b) histological examination of gross sections of vaginal mucosa removed during plastic procedures and (c) studies of the stained vaginal smears, all with reference to the time interval spaced between two menstrual episodes.

The vaginal smear method advanced by Papanicolaou and Shorr with H. Traut and J. V. Meigs as chief protagonists is obviously more practical than vaginal biopsy since the specimen to be examined may be secured by the patient at her convenience and brought to the gynecologist daily or at stated intervals. Despite the hardship entailed by daily or frequent calls at the physician's office the knowledge gained in the hands of experienced histologists is enough to compensate in selected cases for the trouble involved. The reward of this time-robbing procedure is identification of the best time for copulation, namely the time immediately preceding and coincident to and immediately after ovulation. The process is tedious, and requires great experience to interpret the smears. The matter of staining is very important. Should this method prove to be universally reliable it may tend in the absence of other more convenient and reliable methods to be worth while teaching individual women of exceptional intelligence, who are keenly bent upon exhausting every measure to help them conceive, how to stain their own specimens and to interpret them, offering them the facilities of clinic or private laboratories. For this interpretation physicians themselves require special training, which takes much time and effort they may not otherwise be able to spare in a busy practice. The women in question may with more leisure and concentrated interest become adept at reading the vaginal smears.

The object of the study of the vaginal smear is obviously to time coital relations to the most fruitful possible time of the menstrual cycle. This holds particularly for the sub-fertile woman whose menses are habitually delayed but may also benefit women who have no menstrual aberrations. While the male gametogenic defect can at once be ascertained by the examination of his semen, ovulation is "notoriously" elusive, taxing the skill of the experts. As is well known, ovulation can

only be discovered directly by search for ova in the opened abdomen, a formidable exploratory procedure to subject the woman to for this sole purpose, the result of which may hold for that particular month. Incidentally should an ovum actually be found in the tube washings during the laparotomy the patient is in no position under the circumstances to take practical advantage of the finding. The evidence therefore must be indirect and simpler to establish.

A second method of estimating cyclical ovarian uterine physiology is based upon examining the cervical mucus. The role of cervical mucus has been the subject of much speculation for a long time before the present era. It was long recognized that it was either favorable or hostile to the reception of spermatozoa. Only in the last two decades has an attempt been made to show that the secretion of cervical mucus undergoes cyclical change in consistency and in amount and that it subserves estrogenic function. Seguy and Vimeux were the first to insist that at ovulation time the cervix mucus is less viscid, more abundant and is transparent favoring the motility of spermatozoa and fostering their progress toward the tubes. Kurzrok and Miller, Lamar, Pommerenke, amongst others, were especially concerned with this question. The evidence adduced points to a great probability that at the time of ovulation the cervical mucus actually is thinner and more abundant and more favorable for the transmission upward of the spermatozoa. Obviously as a practical measure it shares the same disadvantages in that daily visits and examinations are necessary and entails much skillful observation on the part of the physician. As I have previously had occasion to remark in this connection, the best evidence of favorable mucus is the presence in its environment of actively motile spermatozoa—which, however, can be demonstrated at other times than that of the mid-menstrual interval.

A third procedure extremely telltale for the functional status is that which is afforded by endometrial biopsy. For this procedure only one examination per month is necessary. Advantage is taken of the knowledge gained in the past years by countless histological examinations of endometrial curettings. Here too the changes are dependent upon estrogenic function (estrogen, progesterone) both of which are secondary to gonadotrophic-pituitary function. By means of a small curette with or without suction, such as that devised by E. Novak, several small fragments of endometrium are removed from the surface of the uterine

mucosa, which are then subjected to histological examination. The preferred time adopted by most gynecologists, is one to three days before the menses, or a few hours after the actual onset of the menses, which Hamblen resorts to exclusively. If ovulation has taken place the endometrial glands show the typical secretory progestational phase. If ovulation has not taken place, various degrees of proliferation may be exhibited indicating anovulatory menses.

This procedure has two limitations: 1) whatever evidence the endometrial biopsy affords it is restricted to one cycle and is by no means a positive indication that the next or remote menstrual cycles may or may not be ovular or anovular. 2) It is done too long after the event of ovulation to be of practical use. One positive evidence of ovulation however substantiates the existence of a normal functional relationship between ovaries and uterus in the particular woman in question, a condition of primary importance for her reproductive ability. Obtaining the specimen shortly after the onset of the menstrual flow eliminates the possibility of destroying the occasional impregnated ovum which may be thus rudely removed by the curette. More preferable perhaps is the examination of the menstrual discharge collected during the first twelve or twenty-four hours after its onset in a suitable rubber receptacle properly prepared to prevent deterioration.

A fourth procedure resorted to in the past few years has been that of daily temperature recordings throughout the menstrual cycle. This method first promulgated by Zuck and by Rubinstein has become popular since P. Tompkins made available a convenient chart with tracings illustrating the biphasic character of the temperature. Apparently the shift downward by a drop of 6 to 8 tenths of a degree and a similar rise within 24 hours should coincide with the event of ovulation. This method if established on sufficient scientific grounds by correlating adequate evidence adduced by other methods, especially the actual visual demonstration of synchronous ovulation or of pregnancy occurring as a result of a solitary sex act performed according to the indication of the basal temperature, would prove the most practical and so far the most convenient method of determining the actual event of ovulation.

Other methods such as electrical potentiometric determinations, which gave promise at first, but have later proven unreliable, share the inconvenience of daily visits to the physician's office and special elabo-

rate electrical apparatuses, which render it impractical. Another method which has similar disadvantages is hormonal bio-assay. Tedious, expensive and, as yet, subject to too much variation, bio-assays have been more or less abandoned for practical clinical use, except by a few specialists, by university and pharmaceutical laboratories having extensive facilities and personnel. The same disadvantage characterizes kymographic uterotubal insufflation when employed for this special purpose although it is highly suggestive and of scientific interest. Estimating the glycogen content of vaginal, cervical and endometrial mucosa falls into the same category.

Concerning endocrinopathic factors: The freaks are at once recognized. Subjects suffering from classic endocrine disease have been amply described in the literature. Unfortunately the impression has somehow been gained that these freakish individuals preponderate in the sterility group. Actually they are infrequent and form tragic figures because so little can be done for them. This is not to say however that endocrine disorders do not underlie to some extent many otherwise normal looking patients. It is common experience to see one sterile woman after another who differs relatively little by external appearance from fertile members of her sex. The overwhelming majority of my patients have been women who have presented only the slightest stigmata of heterosexual development or virilism. In this respect we would be rather hard put at present if we should depend on hormonal bio-assays to estimate the degree of maleness or femaleness of sterile married couples.

Concerning uterine hypoplasia, much emphasis has been placed upon the uterine index. The convenient hysterometer of Meaker and of Meigs enables one to get an idea of the relative proportion of the length of the cervix and the body of the uterus. Unfortunately, as I have had occasion to point out before, criteria for hypoplasia have not been definitely established. This is of utmost importance. Apart from the theoretical concept of the undeveloped uterus which may resemble the infant's size to that of the prepubertal and early adolescent size, there are encountered many uteri which appear small upon bimanual palpation but which have a length of from 6 to 6½ cm. or even 7 cm. by actual measurement with the uterine sound. From many measurements of uterine length compared to the uterine enlargement of early pregnancy the length of 7 cm. would represent the fully developed, mature uterus; that of 5 cm. or less a hypoplastic uterus. Due allowance must be made for the general body development, size and age of the patient. The size

of the vaginal portion of the cervix and its configuration it seems to me are of considerable importance, perhaps of greater importance than its proportion to the body of the uterus. The short cervix with quadrangular contour instead of the elliptical contour, particularly when its external surface mucosa is still rugous is the best example of the hypoplastic or undeveloped cervix.

What makes determination of the date of ovulation so difficult as compared to the incomparably simple test for tubal patency for example is first, that the ovum is relatively short lived, its longevity not being more than 24 hours to 36 hours; and secondly, it occurs once in 26:28:30 or more days. The claim of some observers that ovulation occurs twice a month or even three times does not make the task easier. Nevertheless one can hope that some reliable simple method of daily examination for evidence of ovulation may yet be achieved.

A fifth procedure previously unknown but available in the past three decades is that afforded by tests for tubal patency. In 1914, Cary first, then Rubin published their first attempts to demonstrate whether fallopian tubes are patent or not patent by injecting x-ray opaque solutions into the uterus under pressure. Since that time many modifications, both in the substances used and the technique, have been advanced. Without going into the reasons which led Rubin away from the early substances used in hysterosalpingography, the latter was succeeded by uterotubal insufflation in 1919. Subsequently an apparatus was developed which, with suitable recording device, resulted in the method of kymographic uterotubal insufflation, using CO_2 as the gas medium. This method enables us to establish patency, non-patency, partial patency (permeable strictures), spasm, and to record the muscular tonicity of the uterus and tubes.

There are two main uses for hysterosalpingography. One is the x-ray visualization of the cavity of the uterus; the other the demonstration of the lumen of the fallopian tubes. As to the first, its value in the investigation of sterility is indisputable. It enables us to diagnosticate obstructive lesions within the uterine cavity not otherwise readily or certainly accessible except by uteroscopy. It also affords us some idea of the developmental status of the uterus. With regard to the second, it is claimed that, not only is the question of patency or non-patency thereby settled, but that the exact site of obstruction is thus localized. Without going into detailed comparison, it may be stated on the basis

of a large and adequately controlled experience that this point can also be diagnosticated by kymographic uterotubal insufflation.

In connection with hysterosalpingograms it must be emphasized that they are subject to the same limitations of subjective interpretation, as in any other department of visceral roentgenology. It obviously takes more knowledge and skill to interpret the results than the mere technical x-ray exposure of the film and its development. Critical review of hundreds of films in the light of the findings of kymographic uterotubal insufflation checked by many laparotomy observations and follow-up records have shown that errors in interpretation of the hysterosalpingogram, both with regard to patency or non-patency, are considerable. The second and chief disadvantage is that when non-resorbable or slowly resorbable x-ray opaque substances are used they may and do produce foreign body reactions with nodulations, which cause permanent occlusion of tubes that were previously only strictured.

With kymographic uterotubal insufflation all these points may be established without the deleterious results just mentioned following hysterosalpingography.

Uteroscopy: Efforts to inspect the interior of the uterus were made before 1914. Hysterosalpingography has since then entirely eclipsed uteroscopy. Inadequate instruments and the necessity of introducing irrigating fluid which would reach the peritoneal cavity and carry possible infection were obstacles that discouraged further attempts to improve upon the David type of hysteroscope. In view of perfected cystoscopes especially of the children's type and advances in our knowledge of the capacity of the uterus, its interior configuration and the pressures usually required for gas or fluid to enter and pass through the tubes, and newer effective chemotherapeutic agents, this method of direct inspection of the uterine cavity in a manner similar to that of cystoscopy has been again undertaken the past few years and I may say with encouraging usefulness.

The instrument employed is that of the narrow gauge McCarthy cystoscope with an acorn attached similar to that employed for uterotubal insufflation. The observation cystoscope is first introduced under irrigation with a maximum pressure of 40 mm.Hg. One need only hold the irrigating bottle at a level of roughly 42 cm. above the patient's body to maintain this maximum pressure. With a forward looking lens both uterine ends may thus be inspected as well as the whole cavity.

The catheterizing cystoscope can next be introduced. With perfected plastic materials now available, the time has come for renewal of attempts to catheterize the uterine ends of the tubes, the accomplishment of which was thought impossible twenty-five years ago. It need only be mentioned that this examination can be made as an office procedure.

With uterotubal insufflation, with hysterosalpingography and uteroscopy, we are now in possession of methods of exploration by which the anatomical continuity of the female genital tract can be established and the functional status also.

There remains only the task of determining the anatomical and functional status of the ovaries. Being concealed and not always palpable on bimanual examination their presence is often assumed by the secondary genital and general manifestations of their endocrine function.

The only practical hint offered by all the investigations including the illuminating work of Hertig and Rock on early impregnated ova is that ovulation usually occurs between 14 and 16 days before the next menstruation. In regular cycles it is easy to anticipate this date. When menstruation is irregular the task becomes very difficult. On the other hand advice to have intercourse 16 to 14 days before the next menses even in women who menstruate regularly, is not uniformly rewarded by success. Moreover, contrary to the Knaus-Ogino theory of the safe period many women conceive at "unorthodox" times, even during menses.

If we have the means to establish the mechanical patency or nonpatency of the upper portion of the female genital tract thus clearing the question as to free or obstructed transportation of the spermatozoa to and through the fimbriated ends of the fallopian tubes—and the same possibility or impossibility for the migration of the ova, we are as yet in no position to determine the physiological function of the ovaries except by the indirect methods already described.

I. Stein and Arens amongst others have sought to combine hysterosalpingography with pneumoperitoneum produced by transuterine insufflation. The shadows obtained by this combined method do not give sufficient detailed data to warrant its extensive use.

Direct inspection of the ovaries has been made possible without laparotomy in its usual sense in two ways: (1) by abdominal peritoneoscopy and (2) by vaginal coelioscopy. The first method is used by a few workers in this country and abroad. It is fraught with somewhat

more danger than the second. Between abdominal peritoneoscopy and a small exploratory laparotomy there is only the difference of two or three inches which in modern surgery is generally regarded as more or less unimportant. Besides, the few inches added to the incision enable the surgeon to perform procedures which may prove useful to the patient.

On the other hand vaginal coelioscopy has the advantage of direct inspection of the ovaries without so much traumatizing of tissues. The posterior vaginal fornix in the knee chest position is relatively thin and allows the instrument of ready introduction into the cul de sac of Douglas. Accidents are not so apt to occur and if they do, are less serious because they occur in the most favorable position for natural drainage. Its limitations are that the posterior cul de sac must be free of adhesions, a handicap which also obtains in abdominal peritoneoscopy.

By vaginal coelioscopy the size and appearance of one or both ovaries may be demonstrated. and in favorable cases, the presence also of corpora lutea in various stages of development. The presence of periovarian adhesions may also be noted. It is a method which we owe to Decker and Cherry who designated it "culdoscopy" and is well worth employing under proper auspices both for scientific and practical purposes in selected cases. Its importance for the future is obviously to serve as a check upon the effect of gonadotrophic hormones in cases of amenorrhea where it may be repeated twice or possibly three times.

Summary

The diagnostic procedures which have been considered in this paper as constituting steps in the investigation of the woman who complains of childlessness need not all be applied to each case. Many women do not need the comprehensive examination as for example when an obvious minor fault is at once discovered, the correction of which suffices; or when there is present a congenital anomaly not amenable to correction; or when azospermia or tubal occlusion has been demonstrated.

I have considered the procedures in toto. A number of these may in many cases be omitted altogether and it has not been my custom to subject each couple to complete investigation at once. Allowed some time, nature can with the proper therapeutic hints accomplish the much desired result.

Investigation can however be underdone as well as overdone. It is

just as erroneous to assume that the husband is "all right" on the say so of the wife, although he is actually aspermic, as it was to accept the old gynecologist's opinion that there was nothing the matter with the wife —although her fallopian tubes were actually occluded. On the other hand it is not necessary in all cases to subject husband and wife to a complete routine physical and laboratory examination, as is insisted upon by some specialists in sterility because the highly specialized techniques are not commensurately rewarded by fruitful results.

For practical purposes a necessary minimum investigation may be adopted which suffices for the majority of cases of sterility. This consists of (1) a good medical and gynecological history, (2) careful general and local physical examination, (3) BMR and other general laboratory blood and urinary examinations, (4) Huhner test and examination of the unmixed specimen of semen, (5) Kymographic Uterotubal Insufflation supplemented when necessary by Hysterosalpingography, (6) basal temperature recording. The essential practical data may be derived from these six steps in the investigation. The others are difficult to carry out or have as yet doubtful practical value. As in all branches of clinical medicine one must in the last analysis exercise clinical judgment in appraising the underlying causes or factors at the basis of the abnormal condition which in the topic under present discussion is genetic failure. Routinization has not in my experience led to more favorable results than judicious selection of the practical measures at our disposal.

In conclusion it should be added that when the minimum investigation as outlined, fails to reveal the faults of fertility then no efforts should be spared to explore all the possibilities of the more elaborate methods of inquiry. There is a special group of sterile couples, about 5 to 10 per cent of all cases, for whose reproductive failure no plausible explanation is as yet to be found. For this relatively small group in particular and to some extent also for the larger group of sterile women much clinical and biologic research remains still to be done.

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CURRENT CONCEPTS OF FERTILITY IN THE MALE*

ROBERT S. HOTCHKISS

Visiting-Surgeon-In-Charge (Urology), Bellevue Hospital

THE acquisition of new knowledge concerning the biochemical constituents of the semen and the metabolic behaviorisms of spermatozoa, suggests the advisability of reviewing this information in respect to clinical applications and to the pursuit of further promising investigations.

The fluid portion of the semen comprises, by far, the bulk of the entire ejaculate. The seminal vesicles contribute the main volume of the discharge exceeding the combined amount from the epididymides, ductus deferentes, prostate and periurethral glands. Analyses of the semen have demonstrated that the fluid is a complex chemical mixture consisting, amongst other elements, of: sodium chloride, phosphates, calcium, sugar, cholesterol, acid phosphatase, ascorbic acid, albumin, globulin, mucin and thromboplastic enzymes. The investigation of Huggins and his associates[1] have demonstrated that the prostate produces little, or no, reducing substances, but elaborates electrolytes and enzymes responsible for the liquification of the semen. Fibrinogen and fibrolysin have been isolated and the lysis of the coagulated semen can be accounted for by their action. It is probable that the coagulation occurs almost immediately upon the emission of the semen from the body but, as yet, this phase of the process is not as clearly understood.

It is difficult to interpret what teleological objective is accomplished in the human by the process of coagulation and liquification of the semen. It is possible that the entire process is merely a phylogenetic phenomenon more clearly represented in the rodents who seal the semen in the vagina by a coagulum called the copulatory plug. However, it is fully appreciated that maximum motility of the spermatozoa is not attained until the lysis of the fresh human ejaculate is completed,

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a process requiring five or ten minutes. The coagulum may offer a protection to the spermatozoa which, for the first time, have come in contact with the utilizable sugar. During lysis they may be offered the opportunity to take advantage of the substrate while being afforded a protection against the acidity of the vagina.

Increased viscosity often has no appreciable deterrent action on the type or duration of motility of spermatozoa. Some specimens of semen having abnormal increased viscosity may exhibit a peculiar clumping or agglutination of sperm resulting in defective motility and an enormous loss of cells due to their entanglement in large clumps. This may represent a faulty operation of the enzyme systems concerned with the production and reversal of the coagulum, but, as yet, the explanation remains theoretical. Additional research may yield valuable means to overcome this relatively rare, but definite, defect in the semen. A promising avenue of investigation remains open.

Experimental observations derived from the study of the metabolism of spermatozoa indicate that the cells have only two known basic requirements. The spermatozoon requires a sugar from which it derives its source of energy, and an isotonic medium furnishing a vehicle for suspension. Ringer's-glucose solution is a simple chemical mixture as contrasted with the impressive array of materials and agents listed above as physiologic constituents of the semen. MacLeod[2] conclusively demonstrated that spermatozoa suspended in sugar-free Ringer's solution lost motility and retained only minimal metabolism after three to six hours. Furthermore, the addition of glucose promptly reactivated the motility and restored normal metabolic rate. Quantitative analyses of reducing substances in semen have shown that 300-600 mgms. per cent are present, whereas only 20 mgms. per cent appears to be the minimal amount of glucose required in Ringer's-glucose solution for maintenance of normal motility and metabolism of spermatozoa. Nature's twenty-fold, or more, excess of foodstuffs over basic requirements may be another illustration of her remarkable extravagance repeatedly exercised in her allotments for the insurance of adequacy in the task of reproduction. A logical deduction from the above would be that possibly poor motility or early inactivation of sperm could be attributed to the absence or reduction of fermentable sugars in semen. A large number of analyses have been done with this presumption in mind, but, in no instance, was there found to be a deficiency approaching the minimal

requirements. It is of interest to note that a large part of the fermentable sugars of seminal fluid is fructose. The epithelium of the seminal vesicles must have the remarkable ability to select substances from the blood stream, or even perhaps, transform glucose into fructose and deposit the substances into the lumen of the vesicles. The seminal vesicles produce all but a fraction of the reducing substances, and as such they are to be considered vital organs in the physiology of reproduction. Doubtless there is purpose for the unexplained complexities of the semen, and it is our ignorance rather than nature's extravagances which causes our concern.

Much remains unknown about the physiology of ejaculation. A study of the divided ejaculate permits speculation on the emptying processes of the ductus deferens, seminal vesicles and prostate.[3] Several men collected the first half of the ejaculate in one test tube and the remainder in a second. Analyses of thirty specimens so obtained are summarized herewith. The initial 39 per cent of the semen contained 76 per cent of all the spermatozoa. The high concentration of reducible substances in the second portion implies that the seminal vesicles emptied during the latter phase of the act. Lactic acid accumulates as an end-product of the glycolytic metabolism of spermatozoa and is found in greater concentration in the denser part of the ejaculate. The motility of the cells is superior in the first portion of the discharge.

From the above, it is possible to infer that, upon discharge of the semen, the ductus deferens empty their ampullae, wherein are stored a dense concentration of sperm ripened for best motility and capable of the highest degree of activity. Thereupon the seminal vesicles discharge their main contribution of reducing substances, along with additional sperm more distally located in the ductus deferens, together with a few poorly motile sperm which may have previously migrated into the vesicles. The prostatic secretions mixed into the combined secretion produce a fairly uniform coagulation. The resultant semen averages two to three cubic centimeters in amounts and, upon liquification, the spermatozoa attack the sugar substrates to obtain energy for motility. Upon deposition into the vagina the semen buffers the hostile vaginal secretions and forms the seminal pool, permitting access and spermigration into the cervix. Lastly, another caprice of nature must occur, for it seems certain that the sperm rapidly leave the elaborate domain of the seminal fluid and enter the cervical canal, carrying very little glu-

cose with them. If several hours elapse before the spermatozoa reach the ovum, then, on the basis of experimental evidence, a new source of energy must be found in the female genital passages. Recent evidence indicates the presence of ample sugar in the cervical mucosa.

The cellular elements of the semen consist mainly of spermatozoa, together with cells which have been detached from the inner walls of the seminal tract and urethra. The process of metamorphosis by which the mature spermatozoon is produced from the undifferentiated germ cell is familiar to all students of the basic sciences. Recently, clinicians have again had occasion to review and reëxamine spermatic tissue, for the procedure of testicular biopsy has become an accepted diagnostic procedure. Testicular biopsy has been utilized to determine whether the absence of spermatozoa in the semen is due to failure of spermatogenesis or to bilateral occlusion of seminal tracts distal to the tubuli efferentes and proximal to the ejaculatory ducts. The history and physical examination may give clues to the cause of the azoospermia, but often it becomes necessary to remove testicular tissue to establish the diagnosis of either seminiferous or obstructive azoospermia.

The study of tubules of the testes removed from men who are sterile has emphasized several important facts which were known to certain pathologists and histologists, but were unappreciated by clinicians. Outstanding among these is the presence of a thickened peritubular membrane about the seminiferous tubule. It has been noted that the degree of atrophy or regression of spermatogenesis is often in direct ratio to the amount of fibrosis developed in the basement membrane. The blood supply to the active spermatic tissue lies in the interstitial areas outside the peritubular membrane and, consequently, it is probable that a barrier is formed preventing proper nutrition or exchange to these cells undergoing mitosis. In addition to the process of spermatogenesis, it is likely that other important steps take place in the tubules equipping the spermatozoon for its ultimate destination—the penetration of the ovum. Pivotal attention is being focused on the structure of the Sertoli cells, to which it is likely all normal sperm must migrate and attach themselves prior to leaving the testes. The histochemists are using their refined techniques to identify the function of the Golgi apparatus, the Charcot crystals and the cholesterol bodies found in these trophic cells. It is possible that this stage of ripening or maturing is essential to the proper endowment or charging of the sperm with

Fig. 1 — Thickened basement membrane with atrophy. Sertoli cells only.

Fig. 2—Seminiferous azoospermia due to incomplete spermatogenesis.

trophic substances which may predetermine its future capacity for motility. Thus we may eventually learn that poor motility might be traced to dysfunction of the Sertoli cells.

Another striking abnormality of tissue removed from men who are without sperm in the semen is a disorderly arrangement of the cells undergoing mitosis. Such tissue offers some opportunity for confusion in deciding if the essential fault is an obstructive lesion, or if the azoospermia is attributable to inadequate spermatogenesis. Often a number of spermatids and a few spermatozoa may be found in some tubules. Nevertheless the usual cellular pattern of a spermatogenesis is disrupted and there is a disorganization of the cells undergoing spermatogenesis. The lumen of the tubules are packed with cells detached in the latter stages of spermatogenesis. The peritubular membrane may be of normal thickness.

The cystological changes in the testes have been dwelt upon and illustrated herewith, for there is a growing appreciation that the great majority of defects found in the semen are traceable to malfunction of the testes. It is quite apparent that abnormal sperm morphology is entirely a testicular fault. Reduced numbers of sperm in the ejaculate

likewise may be attributed to defective spermatic activity. Poor motility, however, has often been considered as a defect due to abnormalities of the prostatic and seminal vesicular secretions. It is probable that a definite proportion of men with this fault have the etiological factor in the spermatic tubules and the spermatozoa are incapable of being stimulated into normal activity upon ejaculation. An analysis of 1500 semen specimens[4] obtained from men whose wives were being investigated for barrenness revealed that, in general, if the cell count were below 60,000,000 per cc. other defects such as motility and abnormal morphology, were more apparent. Semen specimens, in the very low count range, very often exhibited all three deficiencies. Thus, it would appear that faulty spermatogenesis could, in itself, cause oligospermia, increased abnormal forms, and poor motility. Perhaps too often is it assumed that improper motility is evidence of malfunction of the seminal vesicles and prostate.

Accordingly it is pertinent to recall some of the factors exerting an influence or control over spermatogenesis for, by so doing, the rationale of the semen analysis is reviewed and therapeutic inferences are brought into consideration.

It is not beyond the bounds of reality that genetic inheritance may occasionally predetermine spermatic deficiencies. A familiar type of sterility explained by Mendelian laws is the sterile hybrid mule, which is a product of the breeding of the male ass and the domestic mare. A genetic sterility is obviously refractory to any treatment, yet must be considered as a clinical possibility in the human.

There is no evidence that the testes undergo specific changes incident to ageing similar to menopausal changes in the female. Engle[5] found abundant spermatozoa in the testes and ducts of more than one-half of the men past seventy years of age. The testes share the physiological degenerations of senility, such as arteriosclerosis, but no specific alterations associated only with chronological ageing have been identified. Consequently, no serious impairment of the fertility of the middle aged man can be attributed as due to ageing alone.

Nutrition, and its relation to the physiology of the testes, has been studied in detail in the laboratory. Vitamins, minerals and the amino acids are the principal agents tested in the experimental animals. Deprivation of Vitamins A and E has proven to precipitate severe atrophy of germinal epithelium. Vitamins B-complex, C and D are less specific

and effects vary according to species. The amino acids tryptophane, arginine and lysine may be essential for spermatogenesis. The clinical application of this information is restricted for animal tests exhibit marked variation as to species. Individual variation in vitamin utilization in the human is fully recognized. An optimal diet for one individual may be minimal or deficient for another. Intermediary metabolism and the interrelationship of endocrines and vitamins are now appreciated factors in metabolism of vitamins. Some clinical observers suggest that B-complex, or A or E may occasionally benefit poor motility and spermatogenesis, but this is by no means an established clinical fact.

Increased body temperature has conclusively been demonstrated to depress spermatogenesis. The atrophy of cryptorchid testes is well known, presumably from the adverse effect of 2° elevation of temperature over the normal scrotal environment. The clinician should be alert to examine for migratory testes which, in some men, frequently ascend into the warmth of the inguinal regions with change of position. The author is convinced that decisive improvement in the semen has followed the use of measures to prevent the testes from migrating out of the scrotum and into the inguinal canal.

Little precise knowledge is known of the pathology concerning the destructive action upon the testes of the virus producing mumps. It is now known that the epididymis is tremendously inflamed in the acute stage of the so-called "mumps-orchitis," and that the infection which apparently only involves the post-pubital male is in reality an epididymal-orchitis. This infection is undoubtedly the most common and disastrous acute inflammation affecting the testes in the adult. There is no known preventative treatment except the conferred immunity derived from a prepubital attack. The frequent testicular atrophy following severe inflammation of the scrotal contents is well known. Personal observation of men having only clinical parotiditis revealed that several had definite tenderness of the scrotal contents without manifest swelling and local redness of the skin. They may have escaped a clinical diagnosis of epididymal-orchitis, complicating mumps, but the unproven suspicion exists that such might have been a mild type of involvement not without injury to the germinal epithelium.

The deleterious effect of irradiation upon the testes is fully recognized. The arrival of the atomic age ushers in a new appreciation of such danger, for mass sterilization by atomic warfare is now a known

reality. The use of fission material for industrial sources of energy will doubtless be exploited even if atomic energy is prohibited in future wars. Therefore, a new industrial hazard will deserve attention.

The usual consequence of obstruction is atrophy of the secreting organ so affected. The testis, however, retains both its secretory and spermatogenic capacities despite occlusion of the genital passages in the epididymides and ductus deferens. This allows reparative surgery to be employed to relieve the occlusions and reëstablish the patency of the tract upon the supposition that the testes have continued to produce spermatozoa regardless of the length of time the blockage has existed. The operation of vaso-epididymal anastomosis leaves much to be desired, but, when properly employed in appropriate cases, the achievements, when attained, are spectacular and gratifying to those whose sterility is cured. The risk is negligible and, if the procedure fails in purpose, the individual is none the worse than prior to operation.

The problem of the interrelationship of the testes to the other glands of the endocrine system has received enormous attention. The mass of evidence shows that the pituitary exerts a profound effect on the testes and that properly functioning pituitary gland is as necessary for the survival as for the formation of sperm. The thyroid and adrenals, either directly or indirectly, are likewise involved in the endocrine control over the testes. Suffice to state, for this discussion, that there is no effective hormonal treatment for advanced degeneration of spermatic tissue, and that no single hormone or combination of hormones can be regarded as specific for spermatogenesis.

The results of treatment utilizing thyroid substance has won more universal support from the clinicians than any other product of the internal glands. The gonadotropins have had wide usage, but only in exceptional instances are reported as being beneficial. They had best be employed only as measures of last resort. There is no accepted rationale for the use of testosterone propionate which, in the conventional dosages, depresses spermatogenesis. It is with great expectancy that the clinician looks to the research laboratory for future aid in endocrine therapy. Specific discoveries consonant with human physiology, refinement of hormone products, and evaluation of the limitations and indications for organotherapy are essential to the establishment of satisfactory hormone treatment.

It is difficult to provide precise data supporting the theory that

environmental influences producing fatigue, nervous tension, anxiety and overwork are harmful to spermatogenesis. These factors, coupled with the use of alcohol and tobacco, are frequently encountered in the life of the city dweller. Autopsy evidence has proven that the state of spermatogenesis was proportioned to the duration of the disease causing death. Complete testicular atrophy was common following chronic debilitating illness.[6] Susceptible individuals with lowered fertility states are probably injured by excessive fatigue, nervous tension and intemperant use of alcohol and tobacco so that the problem resolves itself into one of individual reaction. Correction of such faults is an integral part of a program designed to promote the best of bodily health and function which is to be shared by the gonads.

It is apparent from this brief discussion that we are as yet only on the threshold of a full appreciation of many vital details of the physiology of the male genital system as related to reproduction. The problems are not those of any one specialty alone, but rather are filled with embarrassing riches to all whose inquisitiveness seeks new ventures. The anatomists, biochemists, histochemists, physiologists, endocrinologists, internists, gynecologists, and urologists have special interest and access to the field, and their combined efforts are essential to the progress which will surely come.

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ORGANIZATION AND ENROLLMENT IN

SECTION ON MICROBIOLOGY

THE Fellowship of the Academy formally approved the organization of the Section of Microbiology at the Stated Meeting, May 1, 1947. The action followed the request submitted to the Council of the Academy by Drs. O. T. Avery, S. Bayne-Jones, M. W. Chase, R. Cole, A. R. Dochez, R. Dubos, K. Emerson, J. Freund, J. Furth, F. Glenn, G. I. Hirst, J. G. Hopkins, F. L. Horsfall, Jr., C. Jungeblut, J. G. Kidd, C. M. MacLeod, J. F. Mahoney, W. McDermott, J. M. McLean, P. McMaster, F. L. Meleney, H. E. Meleney, H. Most, C. Muschenheim, R. S. Muckenfuss, P. K. Olitsky, E. L. Opie, C. P. Rhoads, T. M. Rivers, P. Rous, G. Shwartzman, W. M. Stanley, and H. M. Zimmerman.

The organizers of the Section will serve as officers pro tem until the official elections in May 1948, as follows: Chairman, Gregory Shwartzman; Secretary, Harry Most; and Members of Advisory Committee, Rene J. Dubos, Frank L. Horsfall, Jr., John G. Kidd, Colin M. MacLeod, and Ralph S. Muckenfuss.

The main objectives of the Section shall be to encourage exchange of information among the microbiologists and to facilitate liaison between clinical and laboratory investigators. The programs will be divided into two major groups, namely, those of special nature, primarily intended for the microbiologists; and those of mutual interest to microbiologists, investigators in allied sciences and clinicians. The scope of the Section will embody the following:

1. Bacteriology, Mycology and Parasitology; 2) Viruses and Rickettsiae; 3) Maladies of unknown and uncertain etiology, possibly of infectious origin; 4) Immunology; 5) Chemotherapy; 6) Pathology relative to Microbiology; and 7) Methods of Study adopted from related Sciences, as applied to Microbiology.

Fellows of the Academy interested in microbiology are cordially invited to enroll as members of the Section. This may be accomplished by letter to the Secretary of the Academy requesting such enrollment. As membership in two scientific sections at one time is not permitted under the By-Laws of the Academy, a Fellow desiring to become a member of the Section on Microbiology must tender resignation from membership in the Scientific Section in which he is enrolled, at the same time that he requests membership in this new Section.